However, the phrase "a related reagent" is not found in claim1.

Claim 5 was rejected as being incomplete for omitting the essential step of "synthesizing the compounds to completion". However, the last step in claim 5 (step g) recites that the two prior steps are repeated if necessary "until synthesis of the compounds is complete." Thus, contrary to the Examiner's assertion, claim 5 lacks no essential steps.

The Examiner has also made a number of rejections based on the use of terms such as "first hybridization sequence", "second hybridization sequence", "solid phase reagents", "conditions effective", "for use", "until synthesis of the compounds is complete", "desired compound activity", and "identifying".

It is well settled that the "language of the claims, read in light of the specification" is to be considered whten determining whether the claims are definite. *Allen Archery Inc. v. Browning Mfg. Co.*, 819 F.2d 1087, 2 USPQ 2d 1490, 1494 (Fed. Cir. 1987). The definiteness of the language employed must be analyzed not in a vacuum, but in light of the teaching of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art *In re Angstadt*, 537 F.2d 498, 190 USPQ 214, 217 (C.C.P.A. 1976). Given the Examiner's missunderstanding of the invention and the Examiner's incorrect statements regarding examples in the specification, as described in Section III below, Applicants submit that the Examiner has not established that one of ordinary skill in the pertinent art, when reading the claims in light of the supporting specification, would not have been able to ascertain the claims with a reasonable degree of precision and particularity.

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

III. Rejection Under 35 U.S.C. §112, first paragraph

Claims 1, 5 and 8 were rejected under 35 U.S.C. §112, first paragraph as being enabling for nucleic acids, but not providing reasonable enablement for other compounds. This rejection is traversed in view of the following.

The standard for § 112 enablement is that one skilled in the art would be able to use the description of the invention to make and use the claimed invention without undue experimentation. As stated in M.P.E.P. §2164.01, the fact that experimentation may be complex

does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1987).

More specifically, the Examiner argues that the art is unpredictable because it allows enourmous variability in its applications to novel as well as well known comounds, and that in order to practice the invention as claimed, one skilled in the art would be required to utilize a vast range of compounds outside the family of nucleic acids.

As the Examiner noted, M.P.E.P. §2164.01, outlines the factors to be considered in a determination of undue experimentation, including (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples of the invention; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. See also *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Applicants submit that one of ordinary skill in the art in the art can make and use the claimed invention based on the disclosure in the specification without undue experimentation. With regard to the quantity of experimentation necessary, Applicants point out that, based on the present specification, the quantity of experimentation required to synthesize compounds based on the their nucleic acid tags is routine, and as the Examiner pointed out, "the state of the prior art is replete with number types of compounds synthesized and or utilized in combinatorial solid and liquid phase chemistry." Thus, only routine experimentation is required.

With regard to the amount of direction presented, the specification, taken in conjunction with the teachings of the prior art, provide a great deal of guidance as to how to make and use the claimed compounds. The Examiner asserts that the specification is limited to nucleic acids. However, contrary to the Examiner's assertion, the specification provides a number of working examples. See, for example, the synthesis of polypeptides and peptide libraries (page 11, lines 13 - 17; page 15, line 27 - page 16, line 18), RNA (page 11, line 19), and "small organic molecules, polyketides, subunit oligomers and catalysts for the synthesis of complex molecules from simple substrates, e.g., transition metal mediated reactions termed 'domino' reactions which are highly efficient processes that allow for production of large libraries of complex structures in relatively few steps beginning with simple precursors. See, e.g., Titze and Lieb, *Curr Opin Chem Biol* 2:63-371 (1998)" (page 18, lines 6 - 11). Thus, the tag-directed synthesis of a number of compounds are described in the specification and the prior art is replete with numerous examples.

As regards the nature of the invention, the applicants have discovered a new method for the iterative synthesis of a plurality of compounds wherein a nucleic acid tag directs and encodes the synthesis of the compound to which it is covalently attached. One skilled in the art would understand this method to be a process that will work with a wide variety of compounds synthesized and/or utilized in combinatorial chemistry. As regards the state of the prior art, the Examiner acknowledges that both solid and liquid phase combinatorial chemistry methods were well known. Thus, a great deal was known about synthesizing compounds in a combinatorial manner. The Examiner will also agree that the relative skill of those in the art is quite high.

The breadth of the claims also supports a finding of enablement. The claims require the synthesis of a plurality of compounds utilizing nucleic acid tags that have hybridization sequences and chemical reaction sites, each of which have been defined appropriately.

Taken in conjunction, a consideration of these factors supports a finding of enablement. Applicants submit that even though a large number of possible compounds are encompassed by the claims, this factor is not determinative. As stated above, the standard for § 112 enablement is that one skilled in the art would be able to use the description of the invention to make and use the claimed invention without undue experimentation. Complex experimentation does not make it undue, if the art typically engages in such experimentation. See *M.I.T.,* supra. As further stated above, the techniques for experimental synthesis of compounds in combinatorial chemistry are well known in the art. Accordingly, Applicants submit that the specification fully enables one skilled in the art to make and use the present invention without undue experimentation, thereby satisfying the requirements of 35 U.S.C. § 112, first paragraph.

The Examiner rejected claims 1, 2, 5, 6, 9 and 10 as having a specification enabled for making nucleic acid compounds, but not reasonably providing enablement for methods of tagging or methods of making compounds with tags. This rejection is traversed in view of the following.

Applicants submit that the Examiner has misunderstood the invention. The invention is directed to a method of synthesizing a plurality of compounds wherein a nucleic acid tag directs and encodes the synthesis of the compound to which it is covalently attached. The Examiner asserts that "it would require burdensome experimentation in order to resolve the issue of what's being made, i.e. compounds with tags, or nucleic acid probes." However, there is no mention of making nucleic acid probes in any of the pending claims. The claims are clearly drawn to making

tag-directed compounds.

The Examiner asserts that "the guidance in the specifications [sic] is limited to the process of making nucleic acids using DNA template or tags." This is not correct. As stated above, the example beginning on page 15, line 27 describes a method of making a polypeptide, using the nucleic acid tag to direct the synthesis of the polypeptide. The Examiner claims that the above assertion "is contrary to the language of the claims which describe 'the process of making tags, wherein the tags in each subset has a selected one of a plurality of different first hybridication sequences...'" Forming a nucleic acid tag, however, is not contrary to making a compound wherein the tag directs the synthesis of the compound; it is merely the first step.

In view of the foregoing remarks, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

IV. Rejection under 35 U.S.C. §102

Claims 1-10 were rejected under 35 U.S.C. §102(b) as being anticipated by Brenner and Lerner (1992).

Claims 1-10 were rejected under 35 U.S.C. §102(b) as being anticipated by Lerner *et al.* (U.S. Patent No. 5,723,598).

Claims 1-10 were rejected under 35 U.S.C. §102(b) as being anticipated by Ruth (U.S. Patent No. 5,668,266).

Claims 1-10 were rejected under 35 U.S.C. §102(e) as being anticipated by Van Ness *et al.* (U.S. Patent No. 6,027,890).

These rejections are respectfully traversed in view of the foregoing claim amendments and following remarks.

A. The Claimed Invention

The present invention, as embodied in amended claim 1, is directed to a method of tag-directed synthesis of a plurality of compounds, comprising forming nucleic acid tags, forming reagent-specific compounds on the tags, and then splitting and recombining by differential hybridization of the nucleic acid tags. Thus, the tag directs the synthesis of the compound.

B. The Prior Art

The Brenner and Lerner reference is directed to a process of alternating parallel combinatorial synthesis to encode individual members of a library of chemicals with unique nucleotide sequences. The nature of the chemical structure is decoded by sequencing the nucleotide tag. Nowhere does Brenner and Lerner show or suggest synthesizing compounds wherein the nucleic acid tag directs the synthesis of the compound.

Lerner *et al.* describes the construction of encoded combinatorial chemical libraries where each chemical sequence is labelled by an appended genetic tag to provide a retrogenetic way of specifying each chemical structure. Nowhere does Lerner *et al.* show or suggest synthesizing compounds wherein the nucleic acid tag directs the synthesis of the compound.

Ruth describes a process for chemically synthesizing a modified single-stranded oligonucleotide. Nowhere does Ruth show or suggest synthesizing compounds wherein a nucleic acid tag directs the synthesis of the compound.

Van Ness describes methods for detecting the binding fo ligand pairs. Nowhere does Van Ness show or suggest synthesizing compounds wherein a nucleic acid tag directs the synthesis of the compound.

C. Analysis

"Anticipation requires identity of invention: the claimed invention, as described in appropriately construed claims, must be the same as that of the reference, in order to anticipate." *Glaverbel Societe Anonyme v. Northlake Marketing & Supply, Inc.,* 33 USPQ2d 1496 (Fed. Cir. 1995).

The present invention is directed to a method of forming a plurality of compounds, wherein a nucleic acid tag directs the synthesis of the compound. As described above, none of the references shows or suggests synthesizing compounds wherein a nucleic acid tag directs the synthesis of the compound. Therefore, none of the references anticipate the claimed invention under 35 U.S.C. §102.

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102.

V. Conclusion

In view of the above remarks, the applicants submit that the claims now pending are in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4405.

Respectfully submitted,

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Version with Markings to Show Changes Made

In the Claims:

Claim 1 has been amended as follows:

1. (Amended) A method of tag-directed synthesis of [synthesizing] a plurality of compounds, comprising:

(a) forming a first group of subsets of nucleic acid tags, where the nucleic acid tags in each subset each has a selected one of a plurality of different first hybridization sequences, a mixture of different second hybridization sequences, and a chemical reaction site,

(b) reacting the chemical reaction sites in each of the subsets formed in (a) with a first selected reagent, thereby to form a reagent-specific compound intermediate on the associated sequence in each subset,

(c) forming a second group of subsets of the reacted nucleic acid tags, where the tags in each subset each have a selected one of a plurality of different second hybridization sequences, and a mixture of different first hybridization sequences; and

(d) reacting the compound intermediates in the sequences in each of the subsets formed in (c) with a second selected reagent,

whereby the nucleic acid tags direct the synthesis of the compounds.